IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCE'S

In re application of:	Harry Meade et al.
Serial No:	09/012,904
Filed:	January 23, 1998
For:	TRANSGENIC PRODUCTION OF ANTIBODIES IN MILK
Art Unit:	1636
Examiner:	Celine X. Qian
Attorney Docket Number:	G0744.70014US02

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Dated: September 10, 2008 Signature: Susan Hasbrouck

AMENDED APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Notice of Non-Compliant Appeal Brief mailed April 10, 2008, Appellants submit the following amended Appeal Brief. Appellants have deleted the sentence erroneously indicating that claim 29 has been cancelled. Accordingly the Amended Appeal Brief responds to the Notice. If the Examiner for any reason finds this Amended Appeal Brief to be non-compliant, Appellants respectfully request that she contact the undersigned to expedite consideration of this Appeal originally filed over two years ago on the merits.

Applicant requests a four-month extension of time for filing this response. If there are any additional fees occasioned by this response, including extension fees not covered by the attached credit card payment, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. G0744.70014US02.

This Amended Appeal Brief contains the items required by 37 C.F.R. § 41.37(c)(1), in the order indicated therein.

(i) REAL PARTY IN INTEREST

The real party in interest is GTC Biotherapeutics, Inc., the assignee of record.

(ii) RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no appeals or interferences that may be related to, directly affect, or be directly affected by this appeal.

(iii) STATUS OF CLAIMS

Claims 19, 21, 25-27 and 29-35 are pending in the application. Claims 31-35 are withdrawn as being directed to non-elected matter, so claims 19, 21, 25-27, and 29-30 are on appeal. Claims 1-18, 20, 22-24, and 28 were cancelled during prosecution. No other claims were introduced during prosecution.

(iv) STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Office Action mailed April 20, 2005.

(v) SUMMARY OF THE CLAIMED SUBJECT MATTER

The claims on appeal are directed to a DNA construct for producing recombinant immunoglobulin molecules in the milk of transgenic non-human mammals, as well as cells comprising the DNA. The claimed invention was developed despite the known problems that transgenic animals have with the expression of fusion proteins generally, and the difficulties associated with the production and assembly of biologically active immunoglobulins specifically. [Specification at p. 3, lines 1-10.]

Two teachings in the art counseled against Appellants' invention. First, those of ordinary skill in the art had confronted certain difficulties in producing immunoglobulins in cells other than B-lymphocytes. These difficulties included the following: 1) both heavy and light chains of the desired immunoglobulin must be co-expressed at appropriate levels; 2) nascent immunoglobulin polypeptides undergo a variety of co- and post-translational modifications that may not occur with sufficient fidelity or efficiency in in vitro cell cultures; 3) immunoglobulins require accessory proteins for their assembly; 4) the synthetic and expression capacity of in vitro cell cultures may be inadequate for the large amount of antibody needed commercially; and 5) the expressed recombinant immunoglobulins may be unstable in the extracellular milieu of a foreign cell. [Specification at p. 1, lines 8-22.]

Second, those of ordinary skill in the art had only been able to express single chain polypeptides in the milk of transgenic animals. There had not been a report of successful expression in transgenic milk of a molecule that required multimerization and/or assembly, such as an immunoglobulin. [Specification at p. 2, lines 19-34.]

At the time of Appellants' invention, numerous scientists had attempted to express immunoglobulins in transgenic animals, but those attempts were limited to expression in blood. [Specification at p. 2, lines 1-5.] Given the difficulties in expressing antibodies recombinantly, combined with the difficulties of expressing multimeric proteins in transgenic milk, those of ordinary skill in the art were not motivated to attempt the production of immunoglobulins in transgenic milk with a reasonable expectation of success.

Appellants' invention, thus, is defined most broadly by sole independent claim 19, which is directed to a DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. [Specification at page 5, line 6-22] The DNA construct comprises:

a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, [Specification at page 6, line 4-14]

an immunoglobulin protein-coding sequence, [Specification at page 5, line 24 through page 6, line 3]

a 3' non-coding sequence; [Specification at page 6, line 18-26]

and a unique restriction site between the promoter and the 3' non-coding sequence, [Specification at page 6, line 15-18]

wherein the immunoglobulin protein-coding sequence is inserted into the restriction site; [Specification at page 6, line 15-18]

and wherein said DNA construct is integrated into the genome of said mammal in such a way that said protein-coding sequence is expressed in the mammary gland of said mammal, [Specification at page 6, line 32 through page 7, line 12]

and secreted from said mammary gland in the milk of said mammal; [Specification at page 7, line 13-19] and,

wherein the expressed immunoglobulin protein sequence is primarily or completely of human origin, [Specification at page 10, line 19-25]

wherein each coding region may be expressed individually [Specification at page 11, line 22-26] and,

wherein the immunoglobulin protein-coding sequence encodes a heavy chain coding region; [Specification at page 11, line 22-33]

wherein said immunoglobulin protein-coding sequence encodes a light chain coding region. [Specification at page 11, line 22-33]

Various promoters can be used in the claimed invention (claims 21 and 25), as well as a certain restriction site (claim 26), and a certain non-coding sequence (claim 27). The claims on appeal are also directed to a mammary epithelial cell comprising such a DNA construct (claims 29-30).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 19 and 25-27 are unpatentable under 35 U.S.C. § 103(a) over Meade et al.[1], taken with DeBoer et al.[2]

B. Whether claim 21 is unpatentable under 35 U.S.C. § 103(a) over Meade et al., taken with DeBoer et al., and further in view of Bischoff et al.[3], Buhler et al.[4], Gordon et al.[5], Ebert et al.[6], and Sinnakre et al.[7]

C. Whether claims 19, 21, 25-27, and 29-30 are unpatentable under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

D. Whether claims 19, 21, 25-27, and 29-30 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite.

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[1] US 4,873,316

[2] US 5,663,076

[3] FEBS Letters, 305: 265-268, 1992.

[4] Bio/Technology, 8: 835-838, 1991.

[5] Bio/Technology, 5: 1183-1187, 1987.

[6] Bio/Technology, 8: 140-143, 1990.

[7] FEBS Letters, 284: 19-22, 1991.

(vii) ARGUMENT

A. Claims 19 and 25-27 are patentable under 35 U.S.C. § 103(a) over Meade et al., taken with DeBoer et al.

The rejection of claims 19 and 25-27 under 35 U.S.C. §103(a) as being obvious in light of Meade et al. and DeBoer et al. should be reversed. As discussed above, the prior art did not teach or suggest the transgenic production of immunoglobulins in milk with a reasonable expectation of success for two reasons. First, recombinant antibodies were hard to produce at the time of the invention in cells other than B-cells because of their complex nature, comprising multiple chains that need to be assembled in the proper orientation and multimerized. Specifically, 1) both heavy and light chains of the desired immunoglobulin must be co-expressed at appropriate levels; 2) nascent immunoglobulin polypeptides undergo a variety of co- and post-translational modifications that may not occur with sufficient fidelity or efficiency in in vitro cell cultures; 3) immunoglobulins require accessory proteins for their assembly; 4) the synthetic and expression capacity of in vitro cell cultures may be inadequate for the large amount of antibody needed commercially; and 5) the expressed recombinant immunoglobulins may be unstable in the extracellular milieu of a foreign cell. [Specification at p. 1, lines 8-22.]

Second, although proteins had been expressed transgenically in milk, only simple proteins had been. Nobody been able to express large a molecule that required multimerization and/or assembly, such as an immunoglobulin. [Specification at p. 2, lines 19-34.]

Both Meade et al. and DeBoer et al. list immunoglobulins in a laundry list of proteins that might be expressed in their methods. [Meade et al. at col. 3, lines 38-39; DeBoer et al. at col. 7, line 8.] That speculation, however, does not render the invention obvious because they do nothing to change the lack of motivation in the art and expectation of success. One of ordinary skill in the art would not have been motivated to attempt to express an immunoglobulin in the milk of a transgenic mammal because of the known difficulties with expressing immunoglobulins in cells other than B-cells, combined with the failure of the art to have expressed a complex, multichain protein in transgenic milk.

While both Meade et al. and DeBoer et al. are US patents, which are relevant as prior art for all that they contain, an obviousness rejection still requires a reasonable expectation of

success. The Examiner has not shown that one of ordinary skill in the art would have had a reasonable expectation of success in producing an immunoglobulin in transgenic milk, and the speculation in Meade et al. and DeBoer et al., which actually produce simple proteins, that immunoglobulins might be produced in that way would not have changed that lack of expectation.

Even if one of ordinary skill in the art would have been motivated to combine the teachings of Meade et al. and DeBoer et al. with a reasonable expectation of success, the combination would not render the claimed in invention obvious. Meade et al. fails to provide or teach the following:

I. Meade et al. fails to teach or suggest that expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade et al., simply fails to contemplate expressing these chains separately;

II. Meade et al., fails to teach a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin species;

III. Meade et al, fails to indicate that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk;

IV. Meade et al., fails to disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site;

V. Meade et al. fails to teach that the claimed construct should have a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted; and,

VI. Meade et al., fails to teach the unique construction of the restriction site–such that it has a coding sequence inserted into the site–that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This construction allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use of a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

DeBoer et al. does not provide what Meade lacks. Importantly, neither Meade et al. nor DeBoer et al. teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. DeBoer also fails with regard to each and every other element called out above as deficient in Meade et al. The lack of even one element I – VI as provided above is sufficient to prevent an obviousness rejection from being maintained.

DeBoer et al. does not make up for any of the other deficiencies of the Meade et al. reference. Specifically, the Examiner asserts that DeBoer et al. at Column 30 lines 45-50 and Figure 7E provides for the development of a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' coding sequence. However, neither the textual citation of DeBoer or the Figure demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted. Therefore, this citation simply does not present the elements of the current invention regarding the production fully-functional, fully-assembled immunoglobulins in transgenic mammalian milk. It does not teach this modification of the prior art. Moreover, it does not teach or suggest any combination with Meade et al.

Accordingly, the rejection of claims 19 and 25-27 under 35 U.S.C. §103(a) as being unpatentable over Meade et al., in view of DeBoer et al. should be reversed.

B. Claim 21 is patentable under 35 U.S.C. § 103(a) over Meade et al., taken with DeBoer et al., and further in view of Bischoff et al., Buhler et al., Gordon et al., Ebert et al., and Sinnakre et al.

Appellants do not contend that the limitations of claim 21 render it separately patentable from claims 19 and 25-27. Accordingly, the rejection of claim 21 under 35 U.S.C. § 103(a) over Meade et al., taken with DeBoer et al., and further in view of Bischoff et al., Buhler et al. , Gordon et al. , Ebert et al., and Sinnakre et al. should be reversed for the same reasons discussed regarding rejection A above.

C. Claims 19, 21, 25-27, and 29-30 are patentable under 35 U.S.C. § 112, first paragraph.

The rejection of claims 19, 21, 25-27, and 30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement should be reversed. The Examiner contends that the specification does not support the individual expression of each immunoglobulin chain (heavy coding region and light coding region) in the same construct. However, the application discloses a cassette containing an immunoglobulin light chain under the control of a promoter [Specification at p. 4, lines 2-5; Fig. 1] and an immunoglobulin heavy chain under the control of a promoter. [Specification at p. 4, lines 2-5; Fig. 1] Thus, each immunoglobulin chain is under the control of its own promoter. Each promoter-immunoglobulin chain, that is, the "promoter-linked light and heavy chain genes" [Specification at p. 11, lines 12-13] were excised from their respective plasmids before microinjection into fertilized mouse eggs.

The light chain and the heavy chain remained linked to its respective promoter, just as they were in Figure 1 (promoter-light chain) and in Figure 2 (promoter-heavy chain). Thus, Figure 3 shows the detection of the heavy chain using "the promoter-linked genes shown in Figures 1 and 2", and Figure 4 shows the detection of the light chain using "the promoter-linked genes shown in Figures 1 and 2." Accordingly, the rejection of claims 19, 21, 25-27, and 29-30 as being unpatentable under 35 U.S.C. § 112, first paragraph, for lack of written description should be reversed.

D. Claims 19, 21, 25-27, and 29-30 are patentable under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 19, 21, 25-27, and 29-30 under 35 U.S.C. § 112, second paragraph, as being indefinite because it is unclear whether the two last wherein clauses are both required or whether they are alternatives. Alternative limitations in claims are the exception, which must be clearly identified as such. *See* MPEP § 2173.04(h) Alternative Limitations ("Alternative expressions are permitted if they present no ambiguity"). Appellants have not clearly identified these two wherein clauses as alternatives, so there is no reason to even suspect that they are alternatives. Both clauses are required.

Appellants submit that the use of multiple wherein clauses is commonly accepted in patent law to require that all wherein clauses be met. Indeed, claim 19 itself contains a total of 6 wherein clauses, only one of which is linked with a conjunctive "and." The Examiner has not found the other 3 wherein clauses without a conjunctive "and" to render the claims indefinite, and similarly the last two wherein clauses do not render the claims indefinite.

While claim 19 may not be very artfully drafted (reflecting amendments made over many years), Appellants submit that one skilled in the art would understand that the claim requires that the cell meeting the limitations of the wherein clause following the transitional phrase "further comprising." Accordingly, the claim is not indefinite.

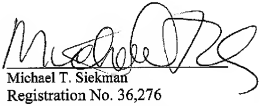
Accordingly, the rejection of claims 19, 21, 25-27, and 29-30 under 35 U.S.C. § 112, second paragraph, as being indefinite should be reversed.

(viii) CONCLUSION

Each of the four rejections on appeal should be reversed for the reasons set forth above, resulting in allowance of claims 19, 21, 25-27, and 29-30.

Respectfully submitted,

Date: 9/10/08

By: 

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CLAIMS APPENDIX

1-18. (Cancelled)

19. (Previously Presented) A DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal comprising a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site; and wherein said DNA construct is integrated into the genome of said mammal in such a way that said protein-coding sequence is expressed in the mammary gland of said mammal, and secreted from said mammary gland in the milk of said mammal; and,

wherein the expressed immunoglobulin protein sequence is primarily or completely of human origin, wherein each coding region may be expressed individually and,

wherein the immunoglobulin protein-coding sequence encodes a heavy chain coding region;

wherein said immunoglobulin protein-coding sequence encodes a light chain coding region.

20. (Cancelled)

21. (Previously Presented) The construct of claim 19 wherein said promoter is selected from the group consisting of a beta lactoglobulin promoter, a whey acid protein promoter, and the lactalbumin promoter.

22-24. (Cancelled)

25. (Previously Presented) The construct of claim 19 wherein said promoter is a casein promoter.

26. (Previously Presented) The construct of claim 19, wherein the restriction site is an XhoI restriction site.

27. (Previously Presented) The construct of claim 19, wherein the 3' non-coding sequence is a 3' non-coding region from a mammary-specific gene.

28. (Cancelled)

29. (Previously Presented) A mammary gland epithelial cell comprising the construct of claim 19 and a construct comprising an immunoglobulin protein-coding sequence which encodes both a light chain and a heavy chain, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains.

30. (Previously Presented) A mammary gland epithelial cell comprising the construct of claim 19 further comprising wherein the cell expresses the light and heavy chains separately and the sequences so expressed are fully human sequences; and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, casein promoter, whey acid protein promoter, and the lactalbumin promoter.

31. (Withdrawn and Previously Presented) A non-human transgenic mammal comprising the insertion of two separate DNA constructs into the genome of said non-human transgenic

mammal such that when both are expressed in combination they provide for the production of a heterologous immunoglobulin in the milk of a non-human transgenic mammal, each said DNA construct comprising a promoter sequence, a DNA sequence providing an immunoglobulin protein-coding sequence, a 3' non-coding sequence for each construct; and a unique restriction site between the promoter sequences and the 3' non-coding sequence;

wherein each of the immunoglobulin protein-coding sequences are inserted into a different vector; and wherein each of the two said DNA constructs are integrated into the genome of said mammal in such a way that a first and a second immunoglobulin protein-coding sequence are expressed in the mammary gland of said mammal, and secreted from said mammary gland in the milk of said mammal; and,

wherein the expressed immunoglobulin protein sequence is primarily or completely of human origin, wherein said first and said second immunoglobulin protein coding region may be expressed individually, and

wherein said first immunoglobulin protein-coding sequence encodes a heavy chain coding region;

wherein said second immunoglobulin protein-coding sequence encodes a light chain coding region.

32. (Withdrawn and Previously Presented) The transgenic mammal of claim 31, further comprising a first vector and a second vector used to insert said first and said second immunoglobulin protein coding regions into the genome of said transgenic mammal.

33. (Withdrawn and Previously Presented) The construct of claim 31 wherein said promoter is selected from the group consisting of a beta lactoglobulin promoter, a casein promoter, a whey acid protein promoter, and the lactalbumin promoter.

34. (Withdrawn and Previously Presented) The construct of claim 31, wherein at least one restriction site is an XhoI restriction site.

35. (Withdrawn and Previously Presented) The constructs of claim 31, wherein the 3' non-coding sequences of each construct are 3' non-coding regions from a mammary-specific gene.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS

None